fibres) compared to only 8.8±4 action potentials/min (n = 18 fibres) in the AZ12606133 treated cohort (Figure B). Movement-evoked nerve firing in AZ12606133 treated animals was approximately 50% of the control group.
Conclusions: Chronic treatment of OA animals with AZ12606133 caused a reduction in articular cartilage destruction as well as attenuating joint nociception. It is possible, therefore, that chondroprotection can have beneficial effects on OA pain severity.

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MMP-13 INHIBITORS REDUCE NOCICEPTION IN A RAT MODEL OF OSTEOARTHRITIS

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Purpose: MMP-13 is a major collagenase in osteoarthritic cartilage, and specific inhibitors of it reduce structural deterioration in animal models of osteoarthritis. Broad-spectrum MMP inhibitors reduce pain behavior as well as structural damage in such models, apparently by independent mechanisms. The purpose of the present study was to determine whether MMP-13-specific inhibitors affect pain behavior in rats following anterior cruciate ligament transection (ACLT), and if so, to begin assessing possible mechanisms of action.
Methods: Three MMP-13 inhibitors were tested, with IC50's against the rat enzyme of 41 (compound A), 7 (compound B), and 4 nM (compound C). All three are at least a thousand-fold less potent against MMPs 1, 2, 3, 8, 9,12, and 14, and all three were negative in assays for inhibition of COX-1 and COX-2. Sprague-Dawley rats were subjected to ACLT in the right knee. The rats were then divided into five groups of 12, 10 of which were used for sensory testing. The groups were dosed orally, b.i.d., beginning the day of surgery, with: vehicle, compound A (60 mg/kg), compound B (30 mg/kg), compound C (30 mg/kg), or meloxicam (a commercially available cyclo-oxygenase inhibitor) (0.5 mg/kg). Laboratory personnel were blinded with respect to compound identity. Once each week following surgery, for 4 weeks, the rats were tested for "use-induced" pain: The length of time required for a tail-flick response to a high-intensity beam of light was determined before and 1, 3 and 6 minutes after repetitive flexion and extension of the right knee. A reduction in the time-to-tail-flick is assumed to reflect pain in the agitated joint. After the final set of these measurements, serum was taken to determine drug levels and the joints were taken for histological analysis.
In*in vitro* experiments, cleavage of pro-IL-1β was detected by western blot and IL-1 activity was determined using Jurkat cells transfected with the IL-1 receptor and a luciferase reporter.
Results: With vehicle-treated rats, joint agitation decreased the time-to-tail-flick at all test times. By the fourth week of the study, all three MMP-13 inhibitors completely eliminated this decrease, as did meloxicam. In the first week, only meloxicam was clearly effective. Compound C was fully effective by the second week, compound B by the third week, and compound A not until the fourth week. The compound that acted most quickly, compound C, was the most potent against MMP-13 and showed the highest serum concentration at the time of sampling. The histological analysis revealed little loss of collagen in this experiment. IL-1β is a known inducer of pain, and in *in vitro* experiments, MMP-13 was found to generate active IL-1β from the precursor.
Conclusions: Inhibiting MMP-13 reduced the pro-nociceptive effects of repetitive flexion and extension of the knee in the rat ACLT model of osteoarthritis. Other MMPs have been reported to induce pain by activating IL-1β, and we found that MMP-13, too, can generate an active form of this cytokine.

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PARTIAL JOINT IMMOBILISATION PROTECTS AGAINST OA AND REVEALS DISTINCT BIOMECHANICAL THRESHOLDS IN THE JOINT

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Purpose: The role of mechanical factors in OA is undisputed, but how these factors drive the processes that lead to joint disease is unknown. What has emerged in recent years is that OA is not simply a disease of cartilage attrition as a result of abnormal or repetitive wearing of the surfaces, but it requires activation of pathways that lead to expression of proteases which degrade the matrix. We used a surgical model of murine OA, induced by destabilisation of the medial meniscus (DMM) to examine the early expression of inflammatory genes in the joints of OA mice and to assess the influence of joint loading on gene expression and the development of OA.
Methods: DMM surgery was performed on 10 week old male C57Bl6 mice or FGF2 null mice by cutting the right menisco-tibial ligament. Some mice underwent sham surgery where the capsule of the joint was opened but the menicso-tibial ligament was left intact. The mice were either left for up to 12 weeks and joints sectioned for histological scoring, or had RNA extracted at early time points post surgery. Microarray analysis was performed and regulated genes were selected and validated quantitatively by RT-PCR using Taqman high density microfluidic cards. A subtotal reduction in weight bearing through the ipsilateral hind limb was induced by cutting the sciatic nerve at the time of DMM surgery. Complete joint immobilisation following DMM surgery was achieved by prolonged anaesthesia.
Results: Compared to sham operated mice, DMM surgery strongly induced a number of genes within 6h of surgery. Of these, the chemokine CCL2, TNF-stimulated gene 6 (TSG-6), IL-6, serum amyloid A (SAA) and arginase 1 were the most highly regulated. Metalloproteinases including ADAMTS4, ADAMTS5 and MMP3 were also regulated. Mice that had undergone sciatic neurectomy exhibited abnormal gait; some weight was born through the limb, but the leg was maintained in full extension and walking was achieved by flexion at the hip. When DMM surgery was performed at the same time as sciatic neurectomy the joints showed no evidence of OA even 12 weeks post surgery. Analysis of early gene expression in these animals revealed a striking abrogation of 70% of the measured genes. Complete joint immobilisation (by prolonged anaesthesia) following DMM surgery abrogated all gene responses in the joint. Those genes that were abrogated by complete immobilisation, but still induced following DMM surgery in neurectomised mice were shown to be highly FGF2-dependent in vivo.
Conclusions: These data show that there is an early inflammatory response in the joint to DMM surgery which is highly mechanosensitive. The selective abrogation of genes following partial and complete joint immobilisation identifies at least two different in vivo mechanical thresholds within the joint, one of which appears to be mediated by FGF2. We hypothesise that exceeding these thresholds determines whether protective or degradative pathways are activated and whether OA develops.

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EFFECTS OF EXERCISE PROGRAM ON PAIN, JOINT STIFFNESS AND PHYSICAL FUNCTION IN ELDERLY PATIENTS WITH KNEE OSTEOARTHRITIS. NURSING-BASED VERSUS HOME-BASED EXERCISE

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Purpose: Osteoarthritis (OA) is a leading cause of pain and disability in elderly people. The knee is the most frequently debilitating joint involved, compromising function and independence. Exercise can be beneficial in reducing physical and functional problems experienced by people with OA. Strength and resistance training are potentially relevant to knee OA because quadriceps weakness has been related to the development and progression of knee OA and is modifiable by training. Therefore, the aims of this study were to evaluate the effects of a progressive 8 weeks resistance-training program in subjects with knee OA with respect to pain, joint stiffness and physical function and to verify if differences exist between exercise done in group by nursing resident's subjects (nursing-based) or individually by subjects living in their own home (home-based).
Methods: Sixty seven subjects (25 men; 42 women) were divided into two groups: an exercise group (ExG) (n=34), mean (SD) age 75.2 (4.9) yr, body mass 72.1 (10.7) kg, height 160.9 (8.4) cm, body mass index (IMC) 27.4 (3.6) $kg \bullet m^{-2}$; and a control group (CG) (n=33), age 74.9 (4.9) yr, body mass 74.1 (4.9) kg, height 160.4 (9.3) cm, body mass index (IMC) 28.5 (4.5) $kg \bullet m^{-2}$. The ExG was divided afterwards in a nursing-based group (n=19; 80.8±6 yr) and a home-based group (n=15; 69.5±3.8 yr). Diagnosis for knee OA was done according to American College of Rheumatology clinical and radiological criteria's. Resistance-training program involved lower extremity exercises, especially for quadriceps strengthening. The participants progressed from completing 2 repetitions per session 2 times per week, to